REMARKS/ARGUMENTS

Request for Continued Examination

Applicants file concurrently herewith a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114. The instant paper is Applicants' required submission under 37 C.F.R. § 1.114 to accompany the RCE.

Status of the Claims

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 stand rejected under 35 U.S.C. § 103(a).

Applicants have amended claim 1, 27, and 30 to point out more distinctly Applicants' claimed invention. In particular, Applicants have amended part (ii) of this claim to recite that the protein "causes expression of said protein from said heterologous nucleic acid" and also to recite that "the enzymatic activity of said protein is the same as the enzymatic activity of said polypeptide". Applicants have amended claim 27 and 30 to be consistent with amended claim 1. Support for the amendment to claims 1, 27, and 30 can be found in Applicants' original disclosure, particularly claim 1 and the specification on pages 5 (line 5), 10 (line 5), and page 11 (first complete paragraph). Additional support for the amendments to claims 27 and 30 can be found in pending claim 1.

Applicants have amended claim 1, 27, and 30 in the interest of expediting examination of instant application and not to limit the scope of their claimed invention. Thus, Applicants expressly reserve the right to file one or more continuing applications or take such other appropriate measures deemed necessary to protect any subject matter that was omitted from the claims by the amendments made herein.

Applicants note for the record that there was a clerical error in claim 1 in the Listing of Claims in the Reply filed March 16, 2010. In that Reply, Applicants did not amend the claims. However, in the fifth line of part (b), Applicants inadvertently omitted the recitation "and an

integrase", which was in the prior version of the claims. Applicants regret this clerical error and any inconvenience that it might have caused the Office.

No new matter has been added by way of amendment of the claim 1.

Reexamination and reconsideration of the application are respectfully requested in view of the following remarks.

The Finality of the Instant Office Action Should Be Withdrawn

Applicants respectfully submit the finality of the instant Office Action is improper for reasons that are discussed below. In the instant Office Action, the Examiner has rejected the claims under a new ground and made the instant Office Action final. In particular, the Examiner has now combined Xu *et al.* (WO 00/71701) with Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO 01/89283) to reject claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 under 35 U.S.C. § 103(a). In the previous Office Action (mailed September 16, 2009), claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 were rejected under 35 U.S.C. § 103(a) based on the combination of only Klimyuk *et al.* and Hooykaas *et al.* (*i.e.*, Xu *et al.* was not applied). In their last response (filed March 16, 2010), *Applicants did not amend the claims*. The Examiner is respectfully reminded that according to M.P.E.P. §706.07(a):

> Under present practice, second or any subsequent actions on the merits shall be final, *except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims*, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

Id. (emphasis added). Applicants further note that the Office Action indicates on page 10 that "**THIS ACTION IS MADE FINAL**" but fails to include any statement or reason why the instant Office Action was made final. Since Applicants' did not amend the claims in their last response and Xu *et al.* was already of record at time they submitted their prior response, the

Examiner failed to comply with M.P.E.P. §706.07(a) when it made the instant Office Action final.

In view of the above remarks, Applicants respectfully submit that it was improper for the Examiner to make the instant Office Action final in view of new ground therein for rejecting claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31. Accordingly, Applicants respectfully request that the Examiner to withdraw the finality of the instant Office Action and to issue a new, non-final Office Action, so as to afford Applicants an initial opportunity to address the rejection of the pending claims under 35 U.S.C. § 103(a) based on this new ground, the combination of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al.* Alternatively, the Examiner is respectfully requested to allow the pending claims.

Applicants further request that the Office refund the fee required for the RCE that was filed concurrently herewith because the filing of the RCE and payment of the fee were made only for the purpose of keeping this application pending but would have not been required but for the improper finality of the instant Office Action.

The Rejection of the Claims Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 are under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO 01/89283) and further in view of Xu *et al.* (WO 00/71701). Claims 1, 27, and 30 have been amended. This rejection is respectfully traversed.

Applicants have amended claim 1, 27, and 30 in the interest of expediting examination of instant application and not to limit the scope of their claimed invention. In particular, Applicants have amended part (ii) of claim 1 to recite that the protein "causes expression of said protein from said heterologous nucleic acid" and also to recite that "the enzymatic activity of said protein is the same as the enzymatic activity of said polypeptide". Applicants have also amended claims 27 and 30 to be consistent with amended claim 1. Applicants believe that the amended claims

are non-obvious over the combination of Klimyuk *et al.*, Hooykaas *et al.* and Xu *et al.* and offer the following remarks in support of the patentability of the amended claims.

In rejecting the claims under 5 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* in view of Hooykaas *et al.* and further in view of Xu *et al.*, the Examiner has relies on Klimyuk *et al.* as the primary reference. The Examiner states on page 3 of the Office Action that the "Klimyuk *et al.* do not teach intein-mediated trans-splicing or the introduction of a polypeptide into the cell" as the difference of the present invention over Klimyuk *et al.* Applicants submit that statement is incorrect and seems to have been copied from the Office Action (see, p. 4) dated March 30, 2010 in U.S. Application No. 10/535,766. Instead, claim 1 differs from Klimyuk *et al.* in that Klimyuk *et al.* does not disclose:

> A method of controlling a genetically-modified multi-cellular plant organism or a part thereof, comprising the following steps:
>
> (a) providing a multi-cellular plant organism or a part thereof, whereby cells of said multi-cellular plant organism or said part contain a heterologous nucleic acid encoding a protein; and
>
> (b) causing expression of the protein from said heterologous nucleic acid in at least some of said cells by delivering a polypeptide to the multi-cellular plant organism or part thereof, said polypeptide rendering said heterologous nucleic acid expressible, said polypeptide being selected from the group consisting of a site-specific recombinase and an integrase;
>
> wherein said protein
>
> (i) contains a protein portion enabling leaving a cell and entering other cells of said multi-cellular plant organism or a part thereof, wherein said protein portion is a domain of a viral movement protein or a domain of a viral coat protein; and
>
> (ii) causes expression of said protein from said heterologous nucleic acid in cells containing said heterologous nucleic acid by a DNA modifying activity of a segment of said protein, said segment being selected from the group consisting of

a site-specific recombinase and an integrase, wherein the enzymatic activity of said protein is the same as the enzymatic activity of said polypeptide.

There is no indication in the methods of Klimyuk *et al.* of a protein having features (i) and (ii), let alone of such protein that is expressed from a heterologous nucleic acid by the action of a site-specific recombinase or an integrase.

The effect of the protein having the portion of item (i) and the enzymatic activity of item (ii) is that the protein can move from cells where it was expressed by the action of the polypeptide of item (b) to neighboring cells of said plant. In neighboring cells, the protein can, due to its enzymatic activity defined in item (ii), act on the heterologous nucleic acid of item (a) and cause expression of more of said protein in these neighboring cells. This process propagates and amplifies the signal initially provided by said polypeptide within the plant, as described in the paragraph bridging pages 5 and 6 of the specification.

Thus, the question is whether Hooykaas *et al.* and/or Xu *et al.*, when combined with Klimyuk *et al.* render obvious the invention. Applicants respectfully submit that this is not the case for the following reasons.

Xu *et al.* relates to trans-splicing, is unrelated to the present invention and does not teach any of the features missing from Klimyuk at al. to arrive at claim 1.

The statement in Klimyuk *et al.*, "A serious concern with prior art virus-based plant expression systems is biological safety" that is cited by the Examiner at the top of page 4 of the Office Action neither provides the missing features, nor does it point the skilled reader to the Hooykaas *et al.* reference. Moreover, the gist of the present invention as explained above with reference to the paragraph bridging pages 5 and 6 of the description does not relate to virus-based plant expression systems, although the cellular process to be controlled by the method of the invention may, of course, be formation of a (viral) amplicon.

The first full paragraph on page 4 of the instant Office Action is unrelated to the present invention and seems to be copied from page 5 of the Office Action dated March 30, 2010 in US No. 10/535,766.

On page 5 of the instant Office Action, the Examiner takes the position that the same control process is used by Hooykaas *et al.* and the invention. However, Hooykaas *et al.* neither teach, nor intend, nor suggest the propagation and amplification effect achieved by the present invention explained above with reference to paragraph bridging pages 5 and 6 of the description. Thus, the fact that the protein of the invention can spread from cell to cell (item (i)) and can cause its expression by the DNA modifying activity defined in item (ii) of claim 1 provides a new quality that is not suggested by Hooykaas *et al.*

At the top of page 6, the Examiner seems to confuse the fusion protein of Hooykaas *et al.* with the heterologous nucleic acid of the invention. The fact that Hooykaas *et al.* suggests two ways for delivering the fusion protein of Hooykaas *et al.* does not suggest anything regarding the heterologous nucleic acid targeted by the cre-recombinase fusion protein of Hooykaas *et al.* Hooykaas *et al.* simply does not consider the heterologous nucleic acid that is the target of the cre recombinase when discussing the fusion protein. Notably, Hooykaas does not suggest that both the fusion protein of Hooykaas *et al.* (if the fusion protein is taken to correspond to the polypeptide of the invention) and a protein encoded by the heterologous nucleic acid should have an enzymatic activity of a site-specific recombinase/integrase.

Hooykaas *et al.* contains very little information on the nucleic acid the Examiner identifies with the heterologous nucleic acid of the invention. On page 4, lines 9-17, it is suggested that a marker gene or antibiotic resistance gene could be removed in the cell to be changed. This is exemplified in the example and Fig. of Hooykaas *et al.*

No other ideas or suggestions are found in Hooykaas *et al.* regarding the heterologous nucleic acid. In the invention, the heterologous nucleic acid encodes a protein having features (i) and (ii) of claim, which is incompatible with marker or antibiotic resistance gene removal suggested by Hooykaas *et al.*

Therefore, it is impossible to arrive at the present invention from a combination of Klimyuk *et al.* and Hooykaas *et al.*, and the addition of Xu *et al.* does not change this situation at all.

A similar issue is brought up the Examiner near the top of page 9 of the Office Action. Here, the Examiner appears to mean that the person having ordinary skill in the art would introduce, based on Hooykaas *et al.*, a heterologous DNA construct encoding the fusion protein and use the heterologous DNA construct at the same time as the heterologous nucleic acid of the invention. The text portion from Hooykaas *et al.* that is cited by the Examiner reads (page 3, lines 17-21):

> The fusion protein to be transferred can either be formed in the transfer system itself, for example, by expressing a vector . . . , or the fusion protein itself may be introduced into the transport system.".

WO 01/89283, p. 3 (emphasis added). The "either . . . or" language of Hooykaas *et al.* rules out the use of the fusion protein in combination with the vector, the latter acting as the heterologous nucleic acid of the present invention. Further, even introducing multiple copies of the vector referred to by Hooykaas *et al.* into a plant, does not lead to the present invention, unless measures are taken that allow the recombinase expressed from the vector to cause expression of more copies of the recombinase from (other copies of) the vector.

If the vector is designed such that the fusion protein of Hooykaas *et al.* can be expressed therefrom without involvement of a recombinase, the recombinase activity of the fusion protein cannot cause expression of the fusion protein (as required by item (ii) of claim 1), because the fusion protein is expressed without involvement of the already expressed fusion protein. Thus, the present invention cannot be arrived at. If, alternatively, the vector mentioned by Hooykaas *et al.* in the text portion cited above requires a recombination reaction before the fusion protein can be expressed, then Hooykaas *et al.*'s embodiment of expressing a vector is not functional because the fusion protein is not expressed (in the absence of a recombinase). Not expressing the fusion protein is, however, contrary to the intention of Hooykaas *et al.* to express the fusion protein from the vector. For providing a recombinase together with the vector, there is no suggestion in Hooykaas *et al.*, and is ruled out by the "either ... or" language as described above. In the absence of any suggestion to this end in Hooykaas *et al.*, it is clear that Hooykaas *et al.* neither suggests such a solution nor does it provide a motivation to do this.

In the absence of a suggestion in Hooykaas *et al.* to make modifications towards the present invention, it is unjustified to require the Applicants to explain why Hooykaas *et al.* does not provide motivation. The Examiner's approach to allege the presence of a motivation based on a text portion Hooykaas *et al.* that cannot be interpreted in the sense of the present invention without contradicting the teaching of Hooykaas *et al.*, and then require the Applicants to show absence of motivation is improper and cannot be relied on to support the rejection of the claims under 35 U.S.C. § 103(a). However, in spite of this, absence of motivation has been shown in the previous paragraph by showing that either the present invention is not obtained or a non-functional embodiment of Hooykaas *et al.* is obtained, *unless the teaching of the present invention is combined with Hooykaas et al. in an impermissible hindsight reconstruction of the present invention.*

For the reasons stated above, the Examiner has failed to state a *prima facie* case of obviousness against the amended claims based on the combination of Klimyuk *et al.*, Hooykaas *et al.* and Xu *et al.* Accordingly, Applicants respectfully request that Examiner withdraw the rejections of the claims under 35 U.S.C. § 103(a).

Status of the Claims of Co-Pending Application No. 10/535,766

The pending claims of co-pending Application No. 10/535,766 (371(c) date June 22, 2005) are drawn to a method of controlling a genetically-modified plant or plant cells and plants and compositions used in this method. The method comprises the steps of: providing a genetically-modified plant or plant cells, wherein the plant or plant cells contain a heterologous nucleic acid encoding a first polypeptide containing or consisting of a first fragment of a protein, said plant or plant cells further containing an additional heterologous nucleic acid that is controlled by an enzymatic activity of said protein; and introducing a second polypeptide into cells of the genetically-modified plant or plant cells by *Agrobacterium* expressibly encoding said second polypeptide, said second polypeptide not being encoded in T-DNA of a Ti-plasmid of said *Agrobacterium*, wherein the second polypeptide contains a second fragment of the protein

and a virE2 or virF peptide sequence enabling the introduction of the second polypeptide into cells of the genetically-modified plant or plant cells, whereby the first fragment and the second fragment jointly generate, only when jointly present, an enzymatic activity of said protein by intein-based trans-splicing, said enzymatic activity being the activity of a site-specific recombinase or integrase; said enzymatic activity triggering formation of a DNA, an RNA or a protein of interest from said additional heterologous nucleic acid. Claim 31 stands rejected under 35 U.S.C. § 112, second paragraph, as being as being indefinite. Claims 1, 3, 5, 7-9, 21, 23-28, and 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO 01/89283) and further in view of Xu *et al.* (WO 00/71701).

Status of the Claims of Co-Pending Application No. 10/535,780

The pending claims of co-pending Application No. 10/535,780 (371(c) date June 22, 2005) are drawn to a method of controlling a controlling a genetically-modified plant and plants and compositions used in this method. The method comprises the steps of providing a genetically-modified transgenic plant, whereby cells of said genetically-modified plant contain a heterologous nucleic acid and whereby the genetically-modified plant is inactive with regard to a cellular process of interest, and switching on the cellular process of interest by directly introducing a polypeptide from a cell-free composition into cells of the transgenic plant containing the heterologous nucleic acid, wherein the polypeptide and said heterologous nucleic acid are mutually adapted such that the polypeptide is capable of switching on the cellular process of interest, wherein the polypeptide comprises a covalently bound membrane translocation sequence enabling the direct introduction of said polypeptide into cells containing said heterologous nucleic acid and the polypeptide has an enzymatic activity of an enzyme selected from the group consisting of a site-specific recombinase and an integrase, wherein said cellular process of interest comprises formation of an expressible RNA amplicon from said heterologous nucleic acid by the enzymatic activity of said polypeptide, said RNA amplicon encoding an RNA-dependent RNA polymerase for amplifying said RNA amplicon and being

capable of cell-to-cell or systemic movement in said plant. Claims 1, 2, 6-8, 11, 13-22, 25-28, and 31 have been determined to be free of the prior art but stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement and written description requirements.

CONCLUSIONS

In view of the above remarks, Applicants submit that the rejections of the claims under 35 U.S.C. § 103(a) are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. § 1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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